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MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER	
DAHLE, CHUN WU	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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	Application No.	Applicant(s)	
Office Action Summary	10/672,280	LAZAR ET AL.	
	Examiner	**Art Unit**	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-134* is/are pending in the application.

4a) Of the above claim(s) *90-102,107,110 and 113-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88,89,103-106,108,109,111 and 112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007, has been entered.

2. Applicant's amendment to the claims, filed October 30, 2007, has been entered.

Claims 1-87 have been canceled.

Claims 88-134 have been added.

Claims 88-134 are pending.

Newly submitted claims 113-134 are directed to an invention that is independent or distinct from the invention originally elected (Group I, drawn to a polypeptide comprising an Fc variant, see Office Action mailed on April 21, 2006) for following reasons:

The invention of the originally elected Group I encompassing now newly added claims 88-112 is related to an antibody or immunoadhesin comprising an Fc variant. The invention of newly added claims 113-134 belongs to Group II (see page 2 of the Office Action mailed on April 21, 2006) that is drawn to a method of treating a mammal by administering an antibody or immunoadhesin comprising an Fc variant. Groups I and II are distinct because the product an antibody or immunoadhesin in Group I can be used for a process of immuno-detection or immuno-purification that is materially different from the claimed method of treating a mammal.

Further, applicant's asserts that all pending claims require amino acid substitution at position 239 of the Fc region, therefore, the search burden for additional species has been

reduced. However, it is noted that this application's claims were subject to an election of species on April 21, 2006. The action specifically stated, on page 4, "Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable...". In response, applicant elected species without traverse of IgG1, position 239D, CD20 antigen, and without an engineered glycoform (see Response to Election/Restriction filed on May 24, 2006), the elected species have been given effect and examined fully with claims drawn to non-elected species held withdrawn from further consideration; these elected species have been rejected under 35 U.S.C. 102(b), 102(e) and 103(a) (see Office Actions mailed on July 26, 2006, November 16, 2006, and August 24, 2007). Because no generic claim was found allowable, the prior art search will not be extended unnecessarily to cover all nonelected species at this time. See MPEP 803.02.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims that are drawn to nonelected invention are withdrawn from consideration. See 37 CFR 1.142(b) and MPEP § 821.03.

Consequently, claims 90-102, 107, 110, 113-134 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 24, 2006.

Claims 88, 89, 103-106, 108, 109, 111, and 112 are currently under consideration as they read on the originally elected invention of Group I and species of IgG1, targeting CD20 antigen, 239D, with no engineered glycoforms.

3. This Office Action is in response to Applicant's amendment to the claims and remarks filed on October 30, 2007.

The rejections of record can be found in the previous Office Actions, mailed February 7, 2005 and October 21, 2005.

4. Applicant's assertion, that provisional application USSN 60/414,433 has support for amino acid substitution 239D in the Fc region, is acknowledged. Upon review of the document, it appears that Figure 2 of USSN 60/414,433 provides support for 239D substitution.

However, it is noted again that claims 88, 108, 109, 111, and 112 do not appear to have adequate support in the priority application USSN 60/414,433 for reasons stated below:

The claimed antibody or immunoadhesin must meet two limitations: (1) comprising any amino acid substitution in position 239 of the Fc region, and (2) increasing the binding to an FcγR. Figures 10 and 11 of provisional application disclose that amino acid substitutions with His (H), Phe (F), Trp(W), and Tyr(Y) in position 239 of the Fc region <u>disfavor</u> Fc/ FcγR complex, thus, such substitutions would abrogate the binding of the Fc to FcγRs (see Figure 10, 11, and Design of Fc variants with abrogated binding to FcγRs on page 7 of the specification). Further, applicant admits that USSN 60/414,433 does not disclose substitutions with Pro (P) and Cys (C) in position 239 (e.g. line 1-6 on page 10 of the Remarks mailed on October 30, 2007). Therefore, substitutions with His, Phe, Trp, and Tyr in position 239 would <u>not</u> yield the claimed antibody or immunoadhesin that has increased binding to an FcγR; and substitution with Pro and Cys at position 239 is not supported by the provisional application. Thus, the provisional application does not appear to provide adequate support under 35 U.S.C. 112 for the claimed

genus of <u>any</u> amino acid substitution in 239 of the Fc region for increased binding to an FcγR. Consequently, claims 88, 108, 109, 111, and 112 are not considered to be entitled to the filing date of the provisional application USSN 60/414,433 (09/27/2002).

5. In view of applicant's amendment to the claims, filed on October 30, 2007, the prior rejection under 35 U.S.C. 102(b) has been withdrawn.

6. In view of applicant's amendment to the claims, filed on October 30, 2007, the prior rejection under 35 U.S.C. 102(e) has been withdrawn.

7. In view of applicant's amendment to the claims, filed on October 30, 2007, the prior nonstatutory obviousness-type double patenting rejections set forth on pages 9-12 of the previous Office Action, mailed on August 24, 2007, have been withdrawn.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 88, 108, 109, 111, and 112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or immunoadhesin, wherein said antibody or immunoadhesin comprises an Fc region wherein the Fc region comprises an amino acid substitution in position 239, wherein the substitution is <u>not</u> S239N, S239F, S239H, S239Y, or S239A, wherein said antibody or immunoadhesin exhibits increased binding affinity to an FcγR, does not reasonably provide enablement for an antibody or immunoadhesin of a parent Fc polypeptide, wherein said antibody or immunoadhesin comprises an amino acid substitution in position 239 of the Fc region, wherein the substitution is S239N, S239F, S239H, S239Y, or S239A, wherein said antibody or immunoadhesin exhibits increased binding affinity to an FcγR. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed.invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in.the art to practice the claimed invention.

Applicant has claimed an antibody or immunoadhesin, wherein the antibody or immunoadhesin comprises an Fc region wherein the Fc region comprises an amino acid substitution in position 239, wherein the antibody or immunoadhesin increases binding to an FcγR compared to antibody or immunoadhesin that does not have amino acid substitution in the Fc region.

The specification discloses the Fc region of IgG antibody interacts with FcγRs that are expressed on effector cells such as macrophages and natural killer cells; formation of Fc- FcγRs complexes recruit these effector cells to sites of bound antigen (e.g. tumor antigen) wherein the effector cells can then execute effector functions such as ADCC to destroy target cells (e.g. tumor cells); the binding affinity of the Fc region to FcγRs appears to correlate with the ADCC function (see paragraph [0005], in particular). Further, the specification discloses computational screening methods to identify the amino acids in the Fc region that can be substitute for enhanced ADCC function and show that the residue in position 239 can altered for altered effector function (e.g. see Table 55 on page 103). Furthermore, applicant provided working examples of amino acid substitution (e.g. S239D) of the Fc region exhibits increased binding affinity to the FcγR (e.g. see paragraph [208]).

However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the specification does not teach that amino acid substitution in position 239 of the Fc region can be substituted with any or all residues to achieve the claimed functional characteristics of increased binding to an FcγR. Based on the disclosure, it is clear

that amino acid substitution S239N, S239F, S239H, or S239Y in Fc region shows reduced binding to FcγR (e.g. see variants 87, 88, 132 and 133 on Table 61 on pages 131 and 132 of the instant specification). Further, Figures 10 and 11 of provisional application USSN (60/414,433 disclose that amino acid substitutions with His (H), Phe (F), Trp (W), and Tyr (Y) in position 239 of the Fc region disfavor Fc/ FcγR complex, thus, such substitutions would abrogate the binding of the Fc to FcγRs (see Figure 10, 11, and Design of Fc variants with abrogated binding to FcγRs on page 7 of the specification of USSN 60/414,433). Furthermore, Presta (US Patent 6,737,056, reference A97 on IDS) teach that S239A displays reduced binding to FcγR (e.g. see Table 6 on columns 57 and 58). Therefore, while certain amino acid substitution in position 239 of the Fc region can result in increased binding affinity between Fc-FcγR (e.g. S239D, see variant 86 on Table 61 on page 132 of the instant specification), it is unpredictable that other substitution including S239N, S239F, S239H, S239Y or S239A would yield an antibody or immunoadhesin that has increased binding to an FcγR.

Thus, one of skill in the art would not know how to use an antibody or immunoadhesin comprising an Fc variant comprising S239N, S239F, S239H, or S239Y for increased binding to FcγR. As such, there is insufficient direction as to how to use an antibody or immunoadhesin, wherein said antibody or immunoadhesin comprises an amino acid substitution in position 239 of the Fc region, wherein the substitution is S239N, S239F, S239H, S239Y, or S239A, wherein said antibody or immunoadhesin exhibits increased binding affinity to an FcγR, as encompassed by the claims.

Further, it is noted that the claims recite "an antibody or immunoadhesin of a parent Fc polypeptide" in the preamble. The genus is polypeptide, "antibody"/"Immunoadhesin" are species of the genus "polypeptide". The claims also read on additional structure on either or both ends of the recited antibody or immunoadhesin. However, it does not appear that the instant specification provides adequate support for an antibody or immunoadhesin of a parent Fc polypeptide. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody or immunoadhesin as broadly as is claimed. It is suggested that the claims to be

amended the claims to delete "a parent Fc polypeptide". In addition, applicant is also suggested to consider setting forth "antibody" and "Immunoadhesin" in separate claims for clarity.

Further, it is noted that claim 109 recites "an antibody fragment". A fragment of the heavy chain can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. There is no support in the specification for linking the variable region to any or all of the myriad "fragments" which are encompassed within this language. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that the specific portion of the human constant region, which the variable region is covalently linked to, be explicitly recited (e.g. antigen binding fragment) within the claim or this language be removed completely in order to obviate this rejection.

In view of the disclosed working example of amino acid substitutions that show opposite effect as the claimed antibody or immunoadhesin, the unpredictability of the art, and the breadth of the claims, one of skill in the art would not know how to use an antibody or immunoadhesin commensurate in scope of the claimed invention.

10. Claims 88, 108, 109, 111, and 112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

The claims encompasses an antibody or immunoadhesin, wherein the antibody or immunoadhesin comprises an Fc region wherein the Fc region comprises an amino acid

substitution in position 239, wherein the antibody or immunoadhesin increases binding to an FcγR compared to antibody or immunoadhesin that does not have amino acid substitution in the Fc region.

There is insufficient written description in the specification as-filed of "an antibody or immunoadhesin of a parent Fc polypeptide, said antibody or immunoadhesin comprising an amino acid substitution at position 239, wherein said antibody or immunoadhesin increases binding affinity to an FcγR" as recited in the instant claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

The claims recite a genus of an antibody or immunoadhesin of a parent Fc polypeptide, wherein the antibody or immunoadhesin comprises an amino acid substitution in position 239, wherein the antibody or immunoadhesin increases binding to an FcγR compared to antibody or immunoadhesin that does not have the amino acid substitution in the Fc region as part of the invention without providing a physical structure or testable functional activity for the claimed antibody or immunoadhesin.

Based on the disclosure, it is clear that amino acid substitutions S239N, S239F, S239H, and S239Y in Fc region show reduced binding to FcγR (e.g. see variants 87, 88, 132 and 133 on Table 61 on pages 131 and 132 of the instant specification). Further, Figures 10 and 11 of provisional application USSN (60/414,433 disclose that amino acid substitutions with His (H), Phe (F), Trp (W), and Tyr (Y) in position 239 of the Fc region disfavor Fc/ FcγR complex, thus, such substitutions would abrogate the binding of the Fc to FcγRs (see Figure 10, 11, and Design of Fc variants with abrogated binding to FcγRs on page 7 of the specification of USSN 60/414,433). Furthermore, Presta (US Patent 6,737,056, reference A97 on IDS) teach that S239A displays reduced binding to FcγR (e.g. see Table 6 on columns 57 and 58).

Applicant has disclosed certain amino acid substitutions in position 239 of the Fc region that can result in increased binding affinity between Fc-FcγR (e.g. S239D, see variant 86 on Table 61 on page 132 of the instant specification). Thus Applicant has disclosed only a limited species of the "antibody or immunoadhsin" comprising amino acid substitution at position 239 of the Fc region. However, applicant is not in possession of an antibody or immunoadhesin, wherein said antibody or immunoadhesin comprises an amino acid substitution in position 239 of the Fc region, wherein the substitution is S239N, S239F, S239H, S239Y, or S239A, wherein said antibody or immunoadhesin exhibits increased binding affinity to an FcγR. The claimed antibody or immunoadhesin lack a common structure essential for their function and the claims do not require any particular structure basis or testable functions be shared by the instant antibody or immunoadhesin.

It does not appear based upon the limited disclosure of antibody or immunoadhesin comprising amino acid substitution such as 239D in the Fc region alone that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosure of the instant specification and the teachings of Presta, showing that substitutions S239N, S239F, S239H, S239Y, or S239A have decreased binding affinity to an FcγR.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

In the absence of disclosure of relevant, identifying characteristics of an antibody or immunoadhesin comprising an amino acid substitution at position 239 of the Fc region, there is insufficient written disclosure under 35 U.S.C. 112, first paragraph.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 88, 108, 109, 111, and 112 are rejected under 35 U.S.C. 102(e) as being anticipated by Presta (US Patent 6,737,056. Reference A97 on IDS).

Presta teaches and claims an antibody including (monoclonal antibody or humanized) or immunoadhesin, wherein the antibody or immunoadhesin comprises a variant Fc region wherein the Fc region comprises amino acid substitution at position 239, wherein the antibody or immunoadhesin exhibits increased binding to FcγRs (e.g. see columns 13, 14, 35, and 36). Presta teaches that the binding sites of human and murine antibodies for FcγRs have been mapped to residues 233-239 (e.g. see second paragraph on column 3).

Claim 13 of the Presta reads as the following:

> "13. A polypeptide comprising a variant Fc region which is not a native sequence Fc region and has increased binding to an Fc gamma receptor (Fc.gamma.R), which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 255, 256, 258,265, 267, 268, 269, 270, 272, 279, 280, 283, 285, 298, 289, 290, 292, 293, 294, 295, 296, 298; 301, 303, 305, 307, 312, 315, 324, 327, 329, 330, 335, 337, 338, 340, 360, 373, 376, 379, 382, 388, 389, 398, 414, 416, 419, 430, 434,435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat."

Further, Presta teaches that the preferred molecular targets of the variants include antibodies against CD20 (see 2nd paragraph of column 30, in particular) and said antibody or immunoadhesin can be formulated into a composition comprising a pharmaceutically acceptable carrier (e.g. see column 42).

Therefore, the teachings of Presta anticipate the claimed invention.

Applicant's arguments in conjunction with the citation of *Ex parte Watkins,* filed on October 30, 2007, have been fully considered but have not been found persuasive.

Applicant arguments regarding the S239D substitution are rendered moot since claims that are drawn to S239D are not rejected under the rejection herein.

Further, applicant's arguments relied on *Ex parte Watkins* are render moot because the opinion of *Ex parte Watkins* has not been designated as precedential opinion and each application must be examined on its own merits.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 88, 89, 103-106, 108, 109, 111, and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Presta (US Patent 6,737,056. Reference A97 on IDS).

The teachings of Presta have been discussed, supra. Given that the antibody or immunoadhesin taught by Presta comprises the same structure of an amino acid substitution at position 239 of the Fc region and function of increased binding to an FcγR as the claimed invention, it would have been inherent properties of the prior art antibody or immunoadhesin to have increased binding to FcγRIIIa for allotype of V158 or F158.

The prior art teachings differ from the claimed invention by not exemplifying amino acids substitution S239D.

However, the key invention of Presta is that he identifies position 239 of the Fc region can be substituted with any other naturally occurring amino acid residues including Asp (D) for increased binding to Fc gamma receptor and therefore enhanced ADCC effect (e.g. see column 12 and paragraphs between Tables in column 20 and claim 13).

Given that Presta identifies that position 239 of the Fc region can be substituted with any other naturally occurring amino acid residues, one of skill in the art would choose from this finite number of identified residues with a reasonable expectation of success absent any objective evidence of unexpected results.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (antibody or immunoadhesin comprising an Fc variant comprising amino acid substitutions S239D) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (methods of making amino acid substitutions at position 239 and method of determining Fc-FcγR binding affinity taught by Presta, e.g. see Example 4 on columns 54-70) with no change in their respective functions and the combination would have yielded nothing more than predictable results of increased binding to an FcγR of the antibody or immunoadhesin comprising an Fc variant compared to the parent antibody or immunoadhesin.

B) Simple substitution of one known element for another to obtain predictable results.

The rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element (existing amino acid Ser (S) in position 239 of the Fc region) with another (Asp (D)), see column 12 and paragraphs between Tables in column 20 of Presta) would have yielded predictable results of increased binding to an FcγR function to one of ordinary skill in the art at them time of the invention.

C) Use of known technique to improve similar products in the same way.

The rationale to support a conclusion that the claims would have been obvious is that a method of enhancing a particular effector function (e.g. ADCC of an antibody) via increased binding affinity of Fc to an FcγR was made part of ordinary capabilities (e.g. amino acids substitution S239D of the Fc region, e.g. see claim 13 of Presta) of one skilled in the art based upon the teachings of Presta. One of ordinary skill in the art would have been capable of applying the known methods of amino acid substitution to make Fc variant S239D of an antibody or immunoadhesin to improve the effector function of the antibody including ADCC and the results would have been predictable to one of ordinary skill in the art.

D) Applying a known technique to a known product ready for improvement to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (amino acid substitution S239D of the Fc region of an antibody) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (e.g. antibody or immunoadhesin) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. amino acid substitutions at position 239 of the Fc region) within his or her technical grasp. This leads to the anticipated success of increased binding of Fc to an FcγR and enhancement of ADCC effect of an antibody or immunoadhesin, it is likely the product not of innovation but of ordinary skill and common sense.

F) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since the improvement of ADCC effect of an antibody with amino acid substitution at position 239 of the Fc region would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of an antibody with improved ADCC effect as claimed. The prior art had recognized the obstacles to be overcome in development of antibody with improved ADCC effect, and had suggested a finite number of amino acid substitutions at position 239 of the Fc region to overcome this obstacles. The claims were obvious because it would have been obvious to try the known methods of amino acid substitutions at position 239 of the Fc region, with a reasonable expectation of success.

In this case, the position 239 of the Fc region taught by Presta provides a point of intervention for altering the efffector function of an antibody. A person of ordinary skill has good reason to pursue the known options, e.g. making S239D (see column 12 and paragraphs between Tables in column 20 of Presta), within his or her technical grasp with reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of

ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdiqital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to improve ADCC effect of an antibody by substituting amino acid residues in position 239 of the Fc region, incorporating amino acid residue D in position 239 of the Fc region would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing antibodies with improved ADCC effect as it reads on the claimed composition comprising an antibody variant.

In conclusion, given that the prior art teaches and claims that position 239 of the Fc region can be substituted for improved ADCC function, the prior art also provides multiple working examples of amino acids substitutions using naturally occurring amino acid residues in the Fc region, it would have been obvious to one of skill in the art at the time of the invention to achieve the predictable results of enhancement of ADCC by making S239D in the Fc region of an antibody or immunoadhesin.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 88, 89, 103-106, 108, 106, 111, and 112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over:

claims 1, 2, 10, 13, 17, and 18 of copending USSN11/124,620,

claims 9-12, and 19 of copending USSN 11/396,495,

claims 1-5, 7-13, 20, and 21 of copending USSN 11/538,406,

claims 1-5, 8-13, 15, 20, and 21 of copending USSN 11/538,411,

claims 1, 4-17, and 20-24 of copending USSN 11/544,165,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/765,402,

claims 2, 13-17, and 38 of copending USSN 11/618,457,

claims 2, 13-17, and 38 of copending USSN 11/618,472,

claims 2, 13-17, and 38 of copending USSN 11/618,488,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/764,001,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/765,353,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/765,390,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/765,402,

claims 1, 3, 5, 6, 9, and 11-13 of copending USSN 11/766,609.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and the copending application claims are drawn to same or nearly the same polypeptide variants with the same modifications to the Fc region at position 239 for altered affinity for FcγRs and effector functions. Given that the polypeptide variants rely on the same amino acid modification, the instant claims would anticipate the copending claims. For example, the instant claims that are drawn to species of antibody or immunoadhesin would anticipate the genus of claims of copending USSN 11/396,495 (drawn to a genus of an Fc variant of a parent Fc polypeptide) or claims of copending USSN 11/483,378 (drawn to a genus of protein).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 88, 89, 103-106, 108, 109, 111, and 112 are directed to an invention not patentably distinct from:

claims 1, 2, 10, 13, 17, and 18 of commonly assigned USSN11/124,620,
claims 9-12, and 19 of commonly assigned USSN 11/396,495,
claims 1-5, 7-13, 20, and 21 of commonly assigned USSN 11/538,406,
claims 1-5, 8-13, 15, 20, and 21 of copending USSN 11/538,411,
claims 1, 4-17, and 20-24 of commonly assigned USSN 11/544,165,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/765,402,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/764,001,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/765,353,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/765,390,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/765,402,
claims 1, 3, 5, 6, 9, and 11-13 of commonly assigned USSN 11/766,609,

for reasons stated above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned USSNs: 11/124,620, 11/396,495, 11/538,406, 11/538,411, 11/544,165, 11/765,402, 11/764,001, 11/765,353, 11/765,390, and 11/765,402, and 11/766,609, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Eileen O'Hara can be reached 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chun Crowder

Patent Examiner

February 1, 2008